REMARKS/ARGUMENTS

Claims 73-81 were examined on the merit in the final Office action mailed July 18, 2008. Claims 1-13 have been previously canceled. Claim 73 has been amended. Support for the amendment can be found in the present application. Accordingly, no question of new matter should arise, and entry of this amendment is respectfully requested.

Claims 14-81 are pending in the application. Claims 14-72 have been previously withdrawn from consideration by the examiner as drawn to the non-elected invention. Applicants specifically reserve the right to file one or more divisional applications to the non-elected subject matter.

By the above amendment, Applicants have rewritten claims 73 to more particularly and distinctly define the invention so as to overcome the technical rejection and to define the invention patentably over the prior art.

The applicants submit the following remarks to address the Examiner's rejection which taken in combination with the amendments presented herewith attempt to address each of the Examiner's concerns.

I. Examiner Interview

Applicants thank Examiners Till and Cole for their courtesy in allowing Applicants' representatives to conduct an Examiner Interview (the "Interview") on September 16, 2008. Applicants further thank the Examiners for their suggestions and insights. In attendance at the Interview (in person) were Examiner Kyle Purdy and Primary Examiner Dr. Lakshmi Channavajjala., and Applicant' representatives Mr. Douglas Robinson and Dr. O.M. (Sam) Zaghmout.

During the interview, Applicants' representatives urged that the combination of references, while teaching many of the aspects of the claimed invention, did not teach or suggest the concept of a dosage form which provided a sustained release of a biguanide with a sustained or immediate release of a sulfonylurea and an intermediate release of

glitazone.

II. Rejection under 35 USC 103(a):

The Examiner has rejected claims 73-81 under 35 U.S.C 103 (a) as being unpatentable over Whitcomb (US6011049 hereafter '049) in view of Timmins et al., (WO99/47128 hereafter '128), Timmins et al., (US6031004 hereafter '004) and Antarkar et al., (US20060057202 hereafter '202).

The Examiner contends that Whitcomb et al., teaches a pharmaceutical combination for treating diabetes wherein the combination includes a glitazone, a biguanide and a sulfonylurea of Claim 70 (Office Action, page 3). The Office (through the Examiner) admits on the record that "Whitecomb fails to teach however the biguanide as being a slow release component, the sulfonylurea as being either slow or immediate release and glitazone as being immediate release" (Office Action, page 3). The Examiner also contends that Timmins et al ('128), Timmins et al. ('004) and Antarkar et al. ('202) disclose these limitations that are not present in Whitcomb et al.

Applicants respectfully traverse this rejection and, to the extent they are maintained with respect to the claims as amended herein, request reconsideration and withdrawal of the rejection.

Initially, it is noted that the Office action has not identified where in Whitcomb et al., Timmins et al ('128), Timmins et al. ('004) and Antarkar et al. ('202), the alleged teaching is to be found on all of the limitations of Claims 73-81. Still further, Applicants have carefully reviewed the remainder of patents to Whitcomb et al., Timmins et al., ('128), Timmins et al., ('004) and Antarkar et al., ('202), and find no teaching of all of the limitations of claims 73-81. Thus, for at least this reason, Whitcomb et al., Timmins et al., ('128), Timmins et al., ('004) and Antarkar et al., ('202), cannot make claims 73-81 obvious. Neither Whitcomb et al., alone or in combination with Timmins et al., ('128), Timmins et al., ('004) and Antarkar et al., ('202), discloses:

a) a slow release component comprising biguanid,

b) a slow release or immediate release component comprising sulfonylurea,

c) an immediate release component comprising glitazone,

wherein, the delivery system released around 30-50% of the slow release component within a period of about 2 to 3 hours and not less than 75% of the slow release component within a period of about 24 hours, characterized in that the delivery system is a fixed dose combination for the treatment of diabetes and its associated disorders.

Furthermore, applicants would like to bring to the attention of the Examiner towards the fact that Whitcomb et al., merely discloses combinations for diabetes containing a sulfonylurea, biguanide, and glitazone. All the components are given as immediate release components.

Timmins et al., ('128) does not mention anywhere in the document many of the limitations of claim 73, namely an oral delivery system comprising combination of a slow release component comprising biguanide,a slow release or immediate release component comprising sulfonylurea and an immediate release component comprising glitazone. Furthermore Timmins et al., ('128) does not mention any teaching that the delivery system releases around 30-50% of the slow release component within a period of about 2 to 3 hours and not less than 75% of the slow release component within a period of about 24 hours, characterized in that the delivery system is a fixed dose combination for the treatment of diabetes and its associated disorders. Instead, Timmins et al., ('128) does teach biphasic controlled release delivery system for the antidiabetic metformin HCl salt, which provides a dosage form that has prolonged gastric residence and includes (1) an inner solid particulate phase formed of substantially uniform granules containing a pharmaceutical having a high water solubility, and one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters, and (2) an outer solid continuous phase in which the above granules of inner solid particulate phase are embedded and dispersed throughout, the outer solid continuous phase including one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials such as one or more waxes, fatty alcohols and/or fatty acid esters,

which may be compressed into tablets or filled into capsules. Timmins et al., ('128) does teach general methods for forming the so-described biphasic controlled release delivery system and using such biphasic controlled release delivery system for treating diabetes. However, there is no teaching on the limitations of the present invention, namely a slow release component comprising biguanide,a slow release or immediate release component comprising sulfonylurea and an immediate release component comprising glitazone. Furthermore, as mentioned above, there is no teaching in Timmins et al., ('128) that the delivery system releases around 30-50% of the slow release component within a period of about 2 to 3 hours and not less than 75% of the slow release component within a period of about 24 hours, characterized in that the delivery system is a fixed dose combination for the treatment of diabetes and its associated disorders.

Timmins et al., ('004) does not mention anywhere in the document many of the limitations of claim 73, namely an oral delivery system comprising combination of a slow release component comprising biguanide,a slow release or immediate release component comprising sulfonylurea and an immediate release component comprising glitazone. Furthermore Timmins et al., ('004) does not mention any teaching that the delivery system releases around 30-50% of the slow release component within a period of about 2 to 3 hours and not less than 75% of the slow release component within a period of about 24 hours, characterized in that the delivery system is a fixed dose combination for the treatment of diabetes and its associated disorders. Instead, Timmins et al., ('004) does teach salts of the antidiabetic agent metformin acre which are metformin salts of dibasic acids (2:1 molar ratio), metformin (2:1) fumarate and metformin (2:1) succinate, that may be employed alone or in combination with another antihyperglycemic agent such as glyburide, for treating diabetes. Timmins et al., ('004) does teach a method for treating diabetes employing the novel metformin salt by itself or in combination with another antidiabetic agent. However, there is no teaching on the limitations of the present invention as claimed, namely a slow release component comprising biguanide,a slow release or immediate release component comprising sulfonylurea and an immediate release component comprising glitazone. Furthermore, as mentioned above, there is no

teaching in Timmins et al., ('128) that the delivery system releases around 30-50% of the slow release component within a period of about 2 to 3 hours and not less than 75% of the slow release component within a period of about 24 hours, characterized in that the delivery system is a fixed dose combination for the treatment of diabetes and its associated disorders.

Antarkar et al. ('202) does teach pharmaceutical composition, comprising of thiazolidinediones and biguanide for controlling hyperglycemia manufactured as multilayer tablet and its process of manufacturing, for immediate release of thiazolidinediones or thiazolidinediones and biguanide and prolonged release of the biguanide only, the tablet comprising of minimum two layers wherein one outer layer comprises of a mixture of excipients and thiazolidinediones or thiazolidinediones and biguanide allowing immediate release of thiazolidinediones or thiazolidinediones and biguanide respectively and the other layer arranged in contact with the immediate release layer which comprises of a novel composition of excipients and a minimum one or more non-biodegradable, inert polymer(s) and the biguanide allowing pH independent prolonged release of the biguanide up to a period of 8-12 hours. The tablets are for once a day dosing. Antarkar et al. ('202) does not mention anywhere in the document many of the limitations of claim 73, namely there is no mention of the type of release of the sulfonylurea compound. Claim 73 provides that the sulfonylurea compound can be either sustained release or immediate. Furthermore Antarkar et al. ('202) does not mention any teaching that the delivery system releases around 30-50% of the slow release component within a period of about 2 to 3 hours and not less than 75% of the slow release component within a period of about 24 hours, characterized in that the delivery system is a fixed dose combination for the treatment of diabetes and its associated disorders.

Applicants want to highlight that subject matter claimed in instant application is related to specific delivery system in a fixed dose combination, wherein release of three different class of drugs having limited window of absorption in a combination is controlled or tailored in such a way so as to provide a dosage form that inherently has a prolonged gastric residence time. Such a delivery system results in improvement of glycemic control in diabetic patients in much better way coupled with adjustment of dosage regimen wherein there is dose reduction for some therapeutic components in combination.

Applicants would like to bring to the attention of the Examiner that its very difficult to achieve the release of three active agents belonging to different classes having limited absorption window and that too in a single combination dosage form as release of one drug is drastically effected by the presence of the other. The delivery system of the instant application provides for slow release with minimal inter-patient variability in pharmacokinetic parameters. So, the distinguishing feature is the specific type of delivery system and not a mere combination or simple controlled release because it is very difficult to tailor the profile of altogether different categories of drug with limited absorption window and that too in a single dosage form which is totally new.

Furthermore, neither Whitcomb et al., ('049) and/or Timmins et al ('128), Timmins et al. ('004) and Antarker et al. ('202) patent(s) teach or motivate one of ordinary skilled in the art to provide an oral delivery system comprising a combination of a slow release component comprising biguanide, a slow release or immediate release component comprising sulfonylurea and an immediate release component comprising glitazone. Hence the invention as claimed in our application is a significant technological advancement over the cited prior art. The Supreme Court's decision in KSR International. Co. v. Teleflex, Inc., et al., 550 U.S.(2007) requires that an Examiner provide "some articulated reasoning with some rationale underpinning to support the legal conclusion of obviousness." (KSR Opinion at p. 14). An Examiner must "identify a

reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does," (KSR Opinion at p. 15). And, the Examiner must make "explicit" this rationale of "the apparent reason to combine the known elements in the fashion claimed," including a detailed explanation of "the effects of demands known to the design community or present in the marketplace" and "the background knowledge possessed by a person having ordinary skill in the art." (KSR Opinion at p. 14). Anything less than such an explicit analysis may not be sufficient to support a prima facie case of obviousness. In January 2008 BPAI decision entitled In re Wada and Murphy reversed a § 103 rejection because the Examiner did not explain where or how cited art taught or suggested all of the features of a claimed invention.

As noted above that the Office Action fails to specifically address even the expressly recited features of the pending independent and dependent claims. Under the Office's policy of compact prosecution, each claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of the application. (MPEP §707.07(g)). It is submitted that the present application is not sufficiently informal, does not present an undue multiplicity of claims, or exhibit a misjoinder of inventions, so as to reasonably preclude a complete action on the merits. Thus, it is submitted that the Office's failure constitutes a failure to expeditiously provide the information necessary to resolve issues related to patentability that prevents the Applicant from, for example, presenting appropriate patentability arguments and/or rebuttal evidence. (See The Official Gazette Notice of November 7, 2003). Additionally, it is submitted that the Office's failure needlessly encourages piecemeal prosecution, which is to be avoided as much as possible. (MPEP §707.07(g)). Accordingly, in the event that the Office maintains the rejection of any of the independent and/or dependent claims, Applicant respectfully requests, in the interests of compact prosecution, that the Office apply art against each feature of each rejected independent and dependent claims, on the record, and with specificity sufficient to support a prima facie case of obviousness.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

It is well known that in order for any prior-art references themselves to be validly combined for use in a prior-art § 103 rejection, *the references themselves* (or some other prior art) must suggest that they be combined. E.g., as was stated in In re Sernaker, 217 U.S.P.Q. 1, 6 (C.A.F.C. 1983):

"[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantages to be derived from combining their teachings." That the suggestion to combine the references should not come from applicant was forcefully stated in Orthopedic Equipment Co. v. United States , 217 U.S.P.Q. 193, 199 (C.A.F.C. 1983):

"It is wrong to use the patent in suit [here the patent application] as a guide through the maze of prior art references, combining the right references in the right way to achieve the result of the claims in suit [here the claims pending]. Monday morning quarterbacking is quite improper when resolving the question of nonobviousness in a court of law [here the PTO]." As was further stated in Uniroyal, Inc. v. Rudkin-Wiley Corp., 5 U.S.P.Q.2d 1434 (C.A.F.C. 1988), "[w]here prior-art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself ... *Something in the prior art must suggest the desirability and thus the obviousness of making the combination.*" [Emphasis supplied.]

In line with these decisions, the Board stated in Ex parte Levengood, 28 U.S.P.Q.2d 1300 (P.T.O.B.A.&I. 1993):

"In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the

relevant teachings of the, applied references in the proposed manner to arrive at the claimed invention. ...

That which is within the capabilities of one skilled in the art is not synonymous with obviousness. ... That one can *reconstruct* and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion unless that logic and reasoning also supplies sufficient impetus to have led one of the ordinary skill in the art to combine the teachings of the references to make the claimed invention.... Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that 'would lead' that individual 'to combine the relevant teachings of the references.' ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done."

In the present case, there is no reason given in the last Office action to support the proposed combination. However the fact that the cited references teach biguanide, sulfonylurea and glitazone is not sufficient to gratuitously and selectively suggest that the one would be led to substitute parts of one reference for a part of another reference in order to meet applicants' novel claimed combination.

The references relied upon fail to provide an adequate basis in evidence to support the Examiner's initial conclusion of obviousness. In short there must be more than merely establishing that the individual components exist in the prior art. There must be something , found in the prior art which would have suggested , led or motivated one skilled in this art to bring those individual components together in the manner presently claimed. The present rejection lacks this aspect.

Applicants respectfully request, if the claims are again rejected upon any combination of references, that the Examiner include an explanation, in accordance with

M.P.E.P. § 706.02. Ex parte Clapp, 27 U.S.P.Q. 972 (P.O.B.A. 1985), and Ex parte Levengood, supra, a "factual basis to support his conclusion that would have been obvious" to make the combination.

It is respectfully requested that this rejection be reconsider and withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance and notification to that effect is earnestly requested. If desired, the examiner is invited to conduct a telephone conference to expedite the prosecution of the subject application. In such a case, the examiner is invited to call the undersigned attorney.

Should any official at the United States Patent and Trademark Office deem that any further action by the Applicants or Applicants' undersigned representative is desirable and/or necessary, the official is invited to telephone the undersigned at the number set forth below.

The Commissioner is herby authorized to charge any fees which may be required regarding this application under 37 CFR §§ 1.16-1.17 or credit any overpayment, to deposit account No. 503321. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, or otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 503321.

Respectfully submitted,

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